SHORT REPORT

Duration of amantadine benefit on dyskinesia of severe Parkinson's disease

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Background: Recent short-term studies suggested that amantadine (Ama) might ameliorate dyskinesia in patients with Parkinson's disease. A double-blind study programmed over 12 months was designed to assess the duration of the antidyskinetic effect of amantadine on levodopa induced dyskinesia.

Methods: 40 patients treated for 7.5 (2.2) years with levodopa (729.3 (199.4) mg/day) and dopaminoagonists, having peak dose or dyphasic dyskinesia with or without pain, were assessed with the Unified Parkinson's Disease Rating Scale subscale IV, Items 32–34, the Dyskinesia Rating Scale and Investigator Global Assessment. Twenty patients received amantadine chloridrate (100 mg) and 20 received a placebo. The Ama or placebo could be withdrawn when scores indicated worsening of dyskinesia, after agreement with the patient.

Results: After 15 days of amantadine treatment there was a reduction by 45% in the total dyskinesia scores. All patients in the placebo group were withdrawn in 1–3 months and all patients in the Ama group were withdrawn in 3–8 months ($p=0.01$, $p<0.001$). Ama withdrawal induced a rebound with increase of dyskinesia by 10–20% in 11 patients.

Conclusion: 300 mg amantadine reduces dyskinesia in Parkinson's disease by approximately 45% but the benefit lasted less than eight months.

Amantadine (Ama) has been used since 1968 for the treatment of Parkinson's disease (PD) and recently some studies suggested that Ama may ameliorate L-Dopa induced dyskinesia.[1–6]

The Cochrane database review on the effect of Ama[7], however, concludes that ''rigorous analysis…reveals insufficient evidence of its efficacy and safety''. A recent evidence based review of the management of Parkinson's disease[8] also reports that although Ama ''is considered efficacious in reducing dyskinesias…data are inadequate to conclude on the long-term efficacy''.

As prior studies were mostly conducted over short periods of less than 1 month[2 4–5] or with intravenous infusion rather than oral drug administrations[3 6 9] we designed a double blind study focused to the duration of the antidyskinetic effect in a current clinical setting, with oral administrations of all drugs.

PATIENTS AND METHODS

Forty patients (24 men, 16 women, mean age 62.7 (5.2) years), who provided informed consent to participate in a 12 months double-blind study, approved by our ethical committee, respecting the declaration of Helsinki,[10] were selected in 3 months from our patient population [11] and according to CONSORT guidelines.[12] All patients were affected by advanced idiopathic Parkinson's disease[13] complicated by motor fluctuations and L-Dopa induced dyskinesia (Hoehn/Yahr stage[14] 2.6 (0.2), L-Dopa daily dose 730 (190) mg, L-Dopa doses per day 5.5 (0.5), disease duration 7.9 (2.2), Universal Parkinson's Disease Rating Scale (UPDRS)[15] motor subscale score 51.9 (8.5)).

Randomisation assigned Ama 300 mg/day or placebo, with a ratio of 1:1 (20 patients per group). 100 mg Ama tablets were triturated and inserted into polyamide capsules, identical capsules containing agar gel were used as placebo. Titration was from 1 to 3 capsules per day over 6 days.

Dyskinesia was assessed by three clinicians, unaware of randomisation with three different scales: firstly, the Unified Parkinson's Disease Rating Scale (UPDRS) subscale IV, item 32–34 considered as a self assessment scale; secondly, the videotaped amended Goetz scale for dyskinesia[16]—Dyskinesias Rating Scale (DRS), a 0–4 point rating scale for each of the limbs, trunk, head, neck, and orofacial region, with a 0.5 point-scoring interval and a maximum score of 28, allowing a videotaped comparison with evaluations at baseline; and thirdly, the Investigator Global Assessment (IGA) of dyskinesia[17 18] reporting the investigator impression of changes after the last evaluation. DRS scores were obtained 40 min and 2.5 hours after the second L-Dopa administration of morning time.

At the end of each assessment patients and caregivers were confronted with UPDRS, DRS and IGA scores, and could decide on their own to withdraw from or continue treatments if rating scores indicated worsening. The primary endpoint of the study was therefore the occurrence of dyskinesia worse than or equal to that recorded before the initiation of treatment.

On 3 days during the week preceding the clinical assessment, all patients, assisted by a caregiver, had to complete correctly the ''on/off'' self rating charts,[17 18] indicating the duration of ''on'' and ''off'' between 6.00 am and 10.00 pm. Every 30 min the patients selected the rating that best described their condition: ''on'' (good mobility), ''intermediate'', ''off'' (bad mobility—blockade), or asleep.

Secondary endpoints were scale score changes and the durations of the ''on'' and ''off'' states.

All patients were assessed with the three different rating methods and with complete UPDRS scales 15 days after titration, every 30 days during the study, one week, and one month after the end of the study.

All patients were on stable treatment dose for the last month prior to baseline evaluations. Current treatment could not be manipulated during the study, L-Dopa intake could be

Abbreviations: Ama, amantadine; ANOVA, analysis of variance; DRS, Dyskinesia Rating Scale; IGA, Investigator Global Assessment; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale

Follow-up evaluations for Ama and placebo group

	Baseline	15 days	30 days	Before withdrawal 60–240 days	1 week after withdrawal	1 month after withdrawal
AMA						
''On'' time (hours)	8.9 (2.4)	9.6 (2.1)	9.9 (1.9)	9.0 (2.3)	9.4 (2.0)	9.1 (2.3)
''Off'' time (hours)	6.4 (2.9)	5.6 (2.5)	4.8 (2.0)	6.1 (2.4)	6.2 (2.1)	6.9 (2.3)
UPDRS I-III	52.9 (8.5)	48.1 (7.8)	47.2 (7.7)	49.7 (7.9)	51.1 (8.8)	51.5 (9.2)
UPDRS IV 32–34	6.7 (2.8)	2.0 (1.1)	2.3 (1.0)	6.1 (2.8)	7.0 (2.9)	6.8 (2.9)
IGA reduction %	–	100	100	0	0	58
unchanged %	–	0	0	6	35	35
increase %	–	0	0	94	65	7
DRS	19.6 (1.2)	10.5 (1.3)	10.3 (1.6)	18.4 (1.5)	22.2 (3.4)	20.4 (1.4)
PLACEBO						
''On'' time (hours)	9.1 (2.1)	9.2 (2.0)	9.1 (2.2)	9.0 (1.9)	9.0 (2.1)	9.0 (1.8)
''Off'' time (hours)	6.2 (2.4)	6.1 (2.1)	6.2 (2.2)	6.3 (2.1)	6.3 (2.3)	6.3 (2.2)
UPDRS I-III	52.7 (8.2)	52.5 (8.3)	52.7 (8.2)	52.8 (8.1)	52.8 (8.2)	52.4 (8.0)
UPDRS IV 32–34	6.6 (2.6)	6.1 (2.4)	6.4 (2.6)	6.7 (2.6)	6.8 (2.4)	6.8 (2.3)
IGA reduction %	–	11	11	0	0	28
unchanged %	–	83	61	61	72	61
increase %	–	6	28	39	28	11
DRS	20.4 (1.9)	20.2 (1.6)	20.0 (1.6)	20.2 (1.5)	20.4 (1.7)	20.9 (1.7)

The patients who withdrew because of side effects other than dyskinesia, (shown in the figure) are omitted from calculations. (Ama, n = 17; placebo, n = 18) Values are mean (SD).

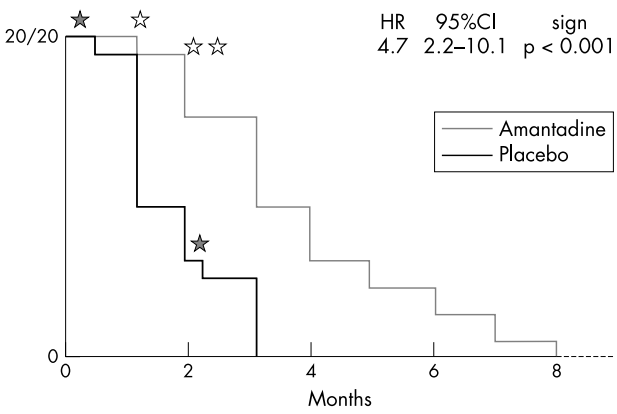
changed only after withdrawal from medications. Side effects were monitored throughout the study.

STATISTICS

A preliminary power analysis of the double-blind comparison of 20 patients per branch indicated that true differences of dyskinesia scores multiplied by 1.055 times the standard deviation, conferred to the study a 0.9 power. Subtotal scores and single items of the UPDRS subscales between treatments and in comparison with baselines and withdrawals were evaluated with the Student's *t* test. Analysis of variance (ANOVA) was used to analyse continuous DRS variables and UPDRS items 32–34 scores. The categorical variables (IGAs) were tested using the Pearson's χ^2 test. Intention to treat analysis was used to compare measurements obtained in the last visit prior to withdrawal. Cumulative time-dependent probabilities of achieving the primary endpoint were calculated by the Kaplan-Meier curve and Cox analysis adjusted for sex. Analyses were performed using SAS 8.1(Cary, NC 27513).

RESULTS

Key variables were equally distributed at baseline in the two groups of patients.



Kaplan-Meier curve indicating the probability of dyskinesia worse than or equal to that recorded before initiation of treatment. Stars indicate drop outs because of side effects unrelated to dyskinesia. Black stars: placebo; white stars: amantadine.

The figure shows a Kaplan-Meier survival curve indicating the time from treatment onset to withdrawal for the Ama and placebo groups. Treatment duration was significantly in favour of the Ama group, $p = 0.01$. Cox analysis adjusted for sex was also significant (3.9; 1.8–12.2). The ''beneficial'' effect of Ama lasted on average 4.9 months, compared with just 1.3 months for the ''placebo effect'', $p<0.001$.

The table reports dyskinesia scores, duration of ''on'' and ''off'', and UPDRS motor scores for all patients completing the study, at baseline, in the first month of treatment, and on the last visit prior to treatment withdrawal (intention to treat), after withdrawal.

Fifteen and 30 days after treatment onset Ama induced reductions of DRS total scores (by 45%) and of UPDRS item 32–34 scores were highly significant compared with baseline and placebo effects ($p<0.001$). IGA scores increased in the Ama group by 2.1 (0.1) points, resulting in a global impression of improvement in all Ama treated patients, while in the placebo group modest decrements of UPDRS item 32–34 scores (8%), reported by two patients, were not paralleled by similar changes of DRS and IGA scores (not significant). UPDRS scale I-III scores and ''off'' time were reduced and ''on'' time was increased in the Ama group. Only UPDRS score reductions were statistically significant versus baseline and placebo ($p<0.01$).

Five patients withdrew because of side effects: one because of tachycardia at 30 days, two at 2 months because of psychosis and livedo reticularis in the Ama group; two in the placebo group because of dizziness (15 days) and somnolence (3 months).

In the following 8 months all Ama patients reported an increase in UPDRS item 32–34 scores, indicating a dyskinesia time increase of 50%: five patients at 3 months, four at 4 months, two at 5 and 6 months, two at 7 months and one at 8 months. DRS and IGA worsening corresponded to subjective reports (see figure and table).

Six placebo group patients withdrew at 1 month, twelve at 2 and 3 months because dyskinesia scores were unchanged or increased by 1 point (DRS or UPDRS 0.6 ± 05) in comparison with baseline.

In the last visit prior to withdrawal no differences with baseline could be evidenced in the Ama and placebo group. DRS and UPDRS scores were modestly lower in the Ama group compared with the placebo (9-6%, not significant).

Following Ama withdrawal, two patients experienced hyperthermia (38.7–39°C), one was severely confused and

therefore Ama was reintroduced; after four days hyperthermia subsided and Ama was gradually introduced over 15 days without further adverse reactions. Eleven patients experienced an abrupt increase of dyskinesia to 100% of daily time. The DRS score was increased by 5.3 (1.8) points (3–9), above the scores reported at last assessments. Worsening subsided in 1–2.5 weeks, with a reduction of daily L-Dopa dose by 10–18% and by fractioning L-Dopa doses to 1 or 2 administrations more than previous daily schedules.

Assessments performed 1 month after withdrawal did not show differences between Ama and placebo group or with baseline for any of the key variables.

A separate analysis was performed on 11 patients who had dyskinesia worsening after Ama withdrawal. The patients had, in comparison to admission, increases of UPDRS total score by 2–5 points, (not significant) versus the scores of the other 9 patients (including the three drop-outs because of side-effects).

DISCUSSION

Our results show that 300 mg/day Ama reduce Parkinson's disease dyskinesia by 45% in the first month of treatment (15 and 30 days), highly significant in comparison with baseline or with placebo.

Three to eight months later the improvements disappeared, as shown by UPDRS items 32–34, DRS and IGA scores. End of study comparisons between Ama and placebo (not significant) and with baseline (not significant) suggest that the appearance of tolerance was not related to disease progression. The study project intended for 1 year was eventually completed in less than 9 months per patient. Furthermore following Ama withdrawal a rebound effect on dyskinesia was observed in 11 patients and in two patients a febrile reaction was observed, both results confirming anecdotal reports in the literature.[6 19 20]

Reductions of dyskinesia by 25–60% were described in the literature for short periods of 2–4 weeks[2 4 5] and in two reports Ama intravenous infusions were used instead of oral administration.[6 9] Only one study describes the long term effect on 13 patients after 1 year, but this study based the evaluation on dyskinesia induced by infusional L-Dopa administration[3] instead of rating the dyskinesia induced by current oral administration.

In early literature the loss of efficacy in 1–12 months is well documented[20 21] and this phenomenon was attributed to tachyphylaxis. This argument has been debated[22] but the present study confirms that tolerance is also observed for specific antidyskinetic effects.

In our study the relatively short effect, with rebound effect of Ama, suggests that the administration of Ama cannot be viewed as a long lasting solution to the occurrence of dyskinesia and fluctuations in patients with severe Parkinson's disease. Its short-term efficacy is however significantly powerful and suggests that further investigations are deserved on drugs acting on the glutamatergic modulation.

The present trial did not assess whether Ama tolerance would respond to dose increases. The dose selected for our study was however the usual clinical dose.[1–6] Higher doses were not considered because the stage and age of patients predicted a higher risk of psychiatric side effects.[23]

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